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Apathy as a Treatment Target in Alzheimer's Disease: Implications for Clinical Trials

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ABSTRACT

Apathy is one of the most prevalent, stable and persistent neuropsychiatric symptom across the neurocognitive disorders spectrum. Recent advances in understanding of phenomenology, neurobiology and intervention trials highlight apathy as an important target for clinical intervention. We conducted a comprehensive review and critical evaluation of recent advances to determine the evidence-based suggestions for future trial designs. This review focused on 4 key areas: 1) pre-dementia states; 2) assessment; 3) mechanisms/biomarkers and 4) treatment/intervention efficacy. Considerable progress has been made in understanding apathy as a treatment target and appreciating pharmacological and non-pharmacological apathy treatment interventions. Areas requiring greater investigation include: diagnostic procedures, symptom measurement, understanding the biological mechanisms/biomarkers of apathy, and a well-

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formed approach to the development of treatment strategies. A better understanding of the subdomains and biological mechanisms of apathy will advance apathy as a treatment target for clinical trials. (Am J Geriatr Psychiatry 2021; ■■:■■−■■)

Highlights

- **What is the primary question addressed by this study?** To determine evidence-based suggestions for future trial designs targeting apathy in neurocognitive disorders by evaluating recent advances in four key areas of progress: assessment, mechanisms/biomarkers, treatment/intervention efficacy, pre-dementia states.
- **What is the main finding of this study?** Considerable progress has been made in understanding apathy as a treatment target and appreciating pharmacological and non-pharmacological apathy treatment interventions. Areas requiring greater investigation include: diagnostic procedures, symptom measurement, understanding the biological mechanisms/biomarkers of apathy, and a carefully considered and well-formed approach to the development of intervention strategies.
- **What is the meaning of the finding?** A better understanding of the subdomains and biological mechanisms of apathy are needed to advance apathy as a treatment target for clinical trials.

INTRODUCTION

Apathy is a common neuropsychiatric symptom (NPS) characterized by a loss of motivation, emotional reactivity and initiative.[1-4] It is one of the most prevalent, stable and persistent NPS observed across the neurocognitive disorders (NCD) spectrum.[5-10] Apathy in NCD is linked to poorer disease outcome, reduced daily functioning, higher levels of caregiver distress, and an increased risk of mortality.[9,11,12]

Apathy is emerging as a treatment target for several reasons. First, apathy is common in NCD such as Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI)[13] and its prevalence increases linearly with disease and time progression.[14,15] Recent meta-analyses found the prevalence of apathy to range from 11%−45% in MCI[16] and from 19%−88% (overall pooled prevalence of 49%) in AD.[17] Population and academic-center based studies (e.g. Alzheimer's Disease Neuroimaging Initiative; ADNI) report prevalence ranging from 3%−51% in MCI and 34%−53% in dementia,[5−7,18] while in clinic and nursing home populations this prevalence increases to 39%−51% and 51%−78% respectively.[8,19,20] Recently, apathy was found to be common among community-dwelling elderly people during the COVID-19 pandemic.[21] Second, apathy is an important marker of increased risk of disease progression,[19,22−25] whether detected in cognitively normal (CN) older adults[22,26,27] or in those with MCI.[23−25] Apathy has been associated with an approximately 2-fold increased risk of dementia in MCI, which was 1) independent of current depression, 2) greater in the short term, and 3) less strong with higher age and greater cognitive impairment.[28] Furthermore, apathy has been linked to a three-fold increased risk of mortality.[9,12] Finally, apathy negatively impacts both patients and caregivers, having been associated with greater functional impairment[29,30] and caregiver burden.[31]

Currently, no medications are approved for the treatment of apathy in NCDs.[32,33] With better understanding of the mechanistic underpinnings of apathy,[34,35] combined with ongoing efforts to refine its diagnostic criteria,[4,36,37] apathy is increasingly becoming a target for clinical trials.[32,33] Recent efforts by key opinion leaders and regulatory officials have led to diagnostic criteria for apathy specifically in neurocognitive disorders, defining it as an indication for treatment.[3,37]

Given the increased interest in and recognition of apathy as an important target for research and intervention,[13] this paper 1) offers a critical evaluation of recent advances in key areas of research focusing on apathy as a treatment target; 2) provides suggestions for future trial designs; and 3) identifies areas of research warranting future attention.

APATHY IN PRE-DEMENTIA STATES

Much of the evidence base for apathy in NCD has been driven by research in AD dementia.[3] Apathy also is a common preclinical and prodromal symptom, and an area of growing interest in advance of dementia[13] but there are issues regarding the definition of apathy and variation in apathy symptoms across the spectrum of cognitive impairment.

Consistent with other NPS, apathy is associated with poorer outcome in pre-dementia populations. Cross-sectionally, apathy in non-demented groups is associated with executive dysfunction,[18,38] poorer quality of life,[39] olfactory disturbance,[40] subjective impairments in physical functioning,[41] impairment in instrumental activities of daily living,[39] and greater family caregiver burden.[42] Longitudinally, apathy in non-demented individuals is associated with functional decline,[43] slowed gait and frailty,[44] and incident cognitive decline and dementia.[23,27,45] Thus apathy is increasingly identified as an important dementia risk marker, whose relevance is highlighted by the inclusion of NPS in the 2011 National Institute on Aging−Alzheimer's Association (NIA-AA) consensus recommendations for diagnosis of all-cause dementia.[46]

To explore the importance of NPS and dementia risk, the NPS Professional Interest Area of the International Society to Advance Alzheimer's Research and Treatment of the Alzheimer's Association (ISTAART-AA) developed research diagnostic criteria for mild behavioral impairment (MBI).[47] Apathy is 1 of the 5 MBI domains. Importantly, the ISTAART-AA MBI criteria specify explicitly that symptoms emerge in later life and persist for ≥6-months in persons without dementia to qualify as MBI. These criteria minimize false positives from the inclusion of reactive symptomatology or medical comorbidity. Also clarified in the ISTAART-AA MBI criteria are the relationship between MCI (which, along with SCD, represents the neurocognitive axis of neurodegenerative disease) and MBI (representing the neurobehavioral axis), allowing for neurocognitive and neurobehavioral syndromes to emerge in parallel or sequentially, with all groups reflecting at-risk states for further cognitive decline and dementia.[48] Prevalence rates of MBI-apathy using a retrospective operationalization matrix have been reported as 20.4% in population-based[49] and 42.2% in clinical samples,[42] and 17%−24% using an MBI-specific assessment tool.[50] In a large study of CN participants, MBI was associated with poorer attention and working memory scores which declined over 1 year.[51] Thus, MBI apathy represents a potential target in disease modifying dementia prevention trials.[52] In addition to associations with cognitive impairment and incident cognitive decline and dementia,[48,53−55] MBI has links to known dementia markers. These markers include amyloid-β,[56,57] tau,[58] neurodegeneration,[59−62] functional dysconnectivity,[63,64] and AD genetic loci.[65,66]

Summary: With the high prevalence of apathy as a preclinical symptom, and the robust evidence for apathy as a prodromal feature, enrolling participants with emergent apathy is both feasible and scientifically sound. Ensuring participation of study partners, who provide the descriptions of apathy, may help overcome difficulties in ensuring those with behavioral apathy or decreased initiative do attend study visits. Emergent apathy in older adults without dementia is a potential treatment target for both pharmacological and non-pharmacological interventions. Treating this clinically significant later life symptom/syndrome will reduce suffering and inform clinicians and researchers on the role of treating late life apathy in dementia risk mitigation.

Assessment

Apathy, considered as a symptom or a syndrome, is a concept still lacking a unified and generally accepted definition. Historic, but somewhat confusing terms, used to either describe apathy or as synonyms of apathy include abulia, indifference, avolition, lack of motivation, flattened affect, social withdrawal, or procrastination. However, update diagnostic criteria have sought to rectify such confusion.[4,37]

While apathy is common in dementia and has been linked to poorer prognosis,[67] its assessment is challenging. Discrepancies in reported prevalence

TABLE 1. Clinical Features Differentiating Apathy from Depression

	Apathy	Depression
Symptomatology		
Affect	Lack emotion	Sad, tearful
Thought content	Does not care	No point to life, pessimistic, hopeless, worthless
Behavior	Passive, compliant	May avoid socialisation or treatment
Suicidality	Not suicidal	Maybe suicidal/"rather be dead"
Anxiety	Not usually anxious	Maybe anxious
Rumination	Usually absent	May be present
Vegetative symptoms	Usually absent although weight loss can occur if lacks initiative to organize meals	Can occur − poor sleep, loss of appetite, weight loss
Longitudinal course	Increases over time if part of a neurodegenerative condition (e.g. dementia)	May resolve or fluctuate; generally diminishes in late stages of a neurodegenerative disease
Treatment Features		
Response to activities	May be amenable to structured activities	May resist structured activities; active avoidance
Counter-transference	No sadness transmits to clinician	Clinician feels sadness and despair
Response to antidepressant medications	Not responsive	May respond

Note. Table of differences in clinical presentation of apathy adapted from Brodaty and Connors.[70]

estimates and frequencies have been attributed to a lack of standardized diagnostic criteria and assessment methods.[68] A particular challenge to apathy diagnostics is its overlap with depression in dementia.

Differentiating Apathy From Depression: Implications For Assessment and Treatment Options

Symptoms of both apathy and depression are associated with many neurological conditions including Parkinson's disease, stroke and all-cause dementia, and psychiatric conditions such as schizophrenia and major depression. Apathy is often misdiagnosed as depression, is common in people with late-life depression and is unresponsive to antidepressants.

While syndromic apathy and depression in dementia share a number of symptoms (lack of interest, lack of initiative, low motivation, decreased libido, decreased concentration and lower energy), there is increasing evidence to indicate that they are distinct, but overlapping entities (see[69] for a detailed review). Clinical differences (Table 1) can assist the differentiation of apathy and depression in dementia,[70] and a key distinguishing feature is that while depression predominantly affects mood, apathy predominantly affects volition.[70] Similarly, treatments of depression such as SSRIs are linked with the onset of a dose-dependent, sometimes reversible, apathy.[71] Further evidence, as detailed below, also supports distinct neuroanatomical pathology, with apathy having been linked to pathology in the left orbitofrontal cortex,[72] right anterior cingulate grey matter,[73] and right fronto-subcortical circuit,[74] while depression appears to be linked to pathology in left dorsolateral prefrontal cortex[72] and orbitofrontal grey matter.[73] It is therefore important to distinguish the two conditions in treatment trials and to specify the context in which apathy occurs, to differentiate apathy from depression, and/or to capture apathy symptomatology within a full depressive disorder. This is particularly important in clinical practice as clinicians often are faced with treating patients exhibiting both dimensions.

Diagnostic Criteria

The conceptualization and measurement of apathy are critical factors in the design of pharmacological and non-pharmacological clinical trials. Apathy should be defined in clinical trials using widely accepted diagnostic criteria. Table 2 provides a summary of the diagnostic criteria and recent revisions aimed at improving care and clinical trial investigation, and aimed to enhance their applicability to diverse clinical populations.

Building on initial attempts to define[2] and operationalize[75] diagnostic criteria for apathy, an international consensus proposed initial diagnostic criteria for the syndrome apathy[76] to be applied in clinical practice independently of its etiology. Those criteria

TABLE 2. Evolution of the Diagnostic Criteria for Apathy

2008 Diagnostic Criteria for Apathy in Alzheimer's disease and other Neuropsychiatric Disorders[76]

For a diagnosis of Apathy the patient should fulfil the criteria A, B, C and D.

Criterion A. Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others

Criterion B. Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time.

Domain B1 - Behaviour

Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:

Initiation symptom: loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)

Responsiveness symptom: loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities)

Domain B2 - Cognition

Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:

Initiation symptom: loss of spontaneous ideas and curiosity for routine and new events (i.e, challenging tasks, recent news, social opportunities, personal/family and social affairs).

Responsiveness symptom: loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person's residence, neighbourhood or community)

Domain B3 - Emotion

Loss of, or diminished, emotion as evidenced by at least one of the following:

Initiation symptom: loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect).

Responsiveness symptom: loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news).

Criterion C. These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

Criterion D. The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).

2018 Proposed New Diagnostic Criteria for Apathy[4]

Criterion A. A quantitative reduction of goal-directed activity either in behavioral, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient himself/herself or by observation of others.

Criterion B. The presence of at least 2 of the 3 following dimensions for a period of at least four weeks and present most of the time

B1. Behaviour & Cognition

Loss of, or diminished, goal-directed behaviour or cognitive activity as evidenced by at least one of the following:

General level of activity: the patient has a reduced level of activity either at home or work, makes less effort to initiate or accomplish tasks spontaneously, or needs to be prompted to perform them.

Persistence of activity: He/she is less persistent in maintaining an activity or conversation, finding solutions to problems or thinking of alternative ways to accomplish them if they become difficult.

Making choices: He/she has less interest or takes longer to make choices when different alternatives exist (e.g., selecting TV programs, preparing meals, choosing from a menu, etc.)

Interest in external issue: He/she has less interest in or reacts less to news, either good or bad, or has less interest in doing new things.

Personal wellbeing: He/she is less interested in his/her own health and wellbeing or personal image (general appearance, grooming, clothes, etc.)

B2. Emotion

Loss of, or diminished, emotion as evidenced by at least one of the following:

Spontaneous emotions: the patient shows less spontaneous (self-generated) emotions regarding their own affairs, or appears less interested in events that should matter to him/her or to people that he/she knows well.

Emotional reactions to environment: He/she expresses less emotional reaction in response to positive or negative events in his/her environment that affect him/her or people he/she knows well (e.g., when things go well or bad, responding to jokes, or events on a TV program or a movie, or when disturbed or prompted to do thing she/she would prefer not to do).

Impact on others: He/she is less concerned about the impact of his/her actions or feelings on the people around him/her.

(*continued*)

TABLE 2. (*continued*)

2008 Diagnostic Criteria for Apathy in Alzheimer's disease and other Neuropsychiatric Disorders[76]	
	Empathy: He/she shows less empathy to the emotions or feelings of others (e.g., becoming happy or sad when someone is happy or sad, or being moved when others need help). *Verbal or physical expressions:* He/she shows less verbal or physical reactions that reveal his/her emotional states. **B3. Social Interaction** Loss of, or diminished engagement in social interaction as evidenced by at least one of the following: *Spontaneous social initiative:* the patient takes less initiative in spontaneously proposing social or leisure activities to family or others. *Environmentally stimulated social interaction:* He/she participates less, or is less comfortable or more indifferent to social or leisure activities suggested by people around him/her. *Relationship with family members:* He/she shows less interest in family members (e.g., to know what is happening to them, to meet them or make arrangements to contact them). *Verbal interaction:* He/she is less likely to initiate a conversation, or he/she withdraws soon from it. *Homebound:* He /She prefer to stays at home more frequently or longer than usual and shows less interest in getting out to meet people.
Criterion C.	These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.
Criterion D.	The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to a diminished level of consciousness, to the direct physiological effects of a substance (e.g. drug of abuse, medication), or to major changes in the patient's environment.
2021 Consensus Diagnostic Criteria for Apathy in Neurocognitive Disorders[37]	
Criterion A. Primary diagnoses	The patient meets criteria for a syndrome of cognitive impairment or dementia (as defined by either ICD or DSM-5 criteria; e.g.: AD, vascular dementia, FTD, DLB, PDD, a pre-dementia cognitive impairment syndrome such as MCI, prodromal AD, or other cognitive disorder).
Criterion B. Symptoms and duration	The patient exhibits at least one symptom in at least two of the following 3 dimensions (B1 to B3). These symptoms have been persistent or frequently recurrent for a minimum of 4 wks and represent a change from the patient's usual behavior. These changes may be reported by the patient themselves or by observation of others. **Dimension B1** Diminished initiative: Less spontaneous and/or active than usual self: Less likely to initiate usual activities such as hobbies, chores, self-care, conversation, work-related or social activities **Dimension B2** Diminished interest: Less enthusiastic about usual activities: - Less interested in, or less curious about events in their environment - Less interested in activities and plans made by others - Less interested in friends and family - Reduced participation in activities even when stimulated - Less persistence in maintaining or completing tasks or activities **Dimension B3** Diminished emotional expression/responsiveness: - Less spontaneous emotions - Less affectionate compared to their usual self - Expresses less emotion in response to positive or negative events - Less concerned about the impact of their actions on other people - Less empathy
Criterion C. Exclusionary criteria	These symptoms are not exclusively explained by psychiatric illnesses, intellectual disability, physical disabilities, motor disabilities, change in level of consciousness, or the direct physiological effects of a substance.
Criterion D. Severity	These symptoms cause clinically significant impairment in personal, social, occupational, and/or other important areas of functioning. This impairment must be a change from their usual behaviour.

Abbreviations: AD: Alzheimer's disease; DLB: dementia with Lewy bodies; DSM: Diagnostic and Statistical Manual of Mental Disorders; FTD: frontotemporal lobar degeneration; ICD: International Classification of Diseases; MCI: mild cognitive impairment; PDD: Parkinson's disease dementia.

were validated in different diseases, and showed good reliability, validity and acceptability.[77] The two most recent revisions apply to apathy in the context of brain disorders[4] or specifically for neurocognitive disorders.[37] These aimed to achieve better adaptation for use in clinical trials and to increase the validity of apathy as a clinical construct by providing a clinical and scientific framework. While the revisions to the diagnostic criteria proposed in 2018[4] preserved the overall diagnostic structure, they included the

following key changes: Criterion A: 1) replacement of the term "motivation" with "goal directed behavior" as this could be measured more objectively; 2) removal of the phrase "which is not consistent with his age or culture" as this was deemed unnecessary when the reduction is compared to the patient's prior level of functioning; 3) addition of the apathy domains of behavior, cognition, emotion and social in the definition. Criterion B: 1) combination of the behavior and cognition domains into a single domain due to challenges with differentiating emotion form behavioral deficits as the cause of the observed behavior decrease; the emotion domain remained unchanged; addition of social interaction as it is proposed to represent a distinct element of apathy;[78] 2) addition of differences between environment-stimulated and self-initiated deficits; 3) addition of examples of symptoms for each area of impairment. Criterion C: unchanged. Criterion D: modification to include significant environmental changes as a potential reason for exclusion, as well as conditions which can mimic apathy, those which are transient and/or are the result of medication. A further advancement, the 2021 Consensus Diagnostic Criteria for Apathy in Neurocognitive Disorders, were developed in collaboration with regulatory authorities and other stakeholders and apply specifically to those with a syndrome of cognitive impairment or dementia.[37] A particular goal was to facilitate use of the criteria among those with either mild or advanced cognitive deficits or physical impairment. The criteria utilize the 3-dimension construct of apathy: diminished initiative/activity, interest/enthusiasm, and emotional expression/responsiveness. Examples are provided for each dimension, including social interactions. While further work is needed to fully validate the criteria, they provide a clear framework for the apathy syndrome among those with cognitive deficits and can aid development of optimal clinical trials.

Rating Scale Aspects

Apart from defining the apathy syndrome, it is equally important to measure its severity to assess the efficacy of interventions. NPS are usually measured with rating scales. Several apathy rating scales have been published, both as independent measurement instruments and as part of general scales measuring a range of NPS (see Supplementary Material 1 for

TABLE 3. Principal Characteristics of Interest for Treatment Studies of the Most Frequently Used Rating Scales for the Measurement of Apathy

	Apathy Evaluation Scale[189]	Neuropsychiatric Inventory: Apathy item[190]	Dementia Apathy Interview and Rating[191]	Apathy Scale[192]	Apathy Inventory[193]	Lille Apathy Rating Scale[194]
Type of scale	Apathy in general	General neuropsychiatric assessment including apathy	Apathy in dementia	Apathy in general	Apathy in general	Apathy in Parkinson's disease
Apathy domains	Yes. 3 domains	No	No	No	Yes. 3 domains	Yes. 9 domains
Sensitivity to change	Yes	Yes	Unknown	Yes	Unknown	Unknown
Time-frame of assessment	4 wks	4 wks	4 wks	4 wks	Not established	4 wks
Information source and type of rater	Patient-rated, informant-rated and clinician-rated versions with semi-structured interview	Clinician-rated through interview with informant. One version (NPI-C) also includes patient's examination	Clinician-rated through structured interview with informant	Clinician-rated through patient or informant interview	Clinician-rated through interview with patient. One version through interview with informant	Clinician-rated through structured interview with patient. One version with structured interview with informant
Specific validation in nursing home patients	Yes (AES-10)	Yes (NPI-NH version)	No	Yes (AS-10-NH version)	No	No

summary). Table 3 shows the main characteristics of interest for treatment studies of the most frequently used apathy rating scales.

Accumulated experience shows that apathy scales should take into consideration:

1 *Psychometric properties.* The scale must have good enough psychometric properties in terms of *quality of its construction, reliability, validity*, and *sensitivity to change* (see below). *Floor and ceiling effects* are particularly important in measuring apathy since apathy is often quite severe in advanced dementia resulting in maximal scores or ceiling effects.
2 *Type of scale.* Apathy rating scales range from general scales to disease- or symptom-specific scales. The *Neuropsychiatric Inventory* (NPI) apathy item and the *Apathy Evaluation Scale* (AES) are the most widely used. These were designed to measure apathy independently of the base disorder and thus offer broad utility but disease-specific scales may have better properties such as greater sensitivity to change and specificity of symptoms. The question about the convenience of developing and using specific scales for individual major diseases or syndromes that cause apathy remains, as do questions about the difference between measuring apathy as symptom or as a syndrome.
3 *Apathy domains.* Apathy is not a single construct; several domains have been proposed depending on different conceptualizations. Marin's model of apathy[1] defined the following domains: emotional response, cognitive activity directed to a specific purpose or goal, and behavior directed to a specific purpose or goal. Levy and Dubois's model[79] defined the domains of emotional blunting, cognitive inertia, and deficit of thinking and self-generated behaviors. Current diagnostic criteria have diminished initiative, diminished interest and diminished emotional expression and/or responsiveness,[37] with social interaction considered under each. Ideally, apathy rating scales should take into account apathy dimensions and be able to measure them independently since they may be associated with different neurobiological changes, and may respond differently to interventions.
4 *Sensitivity to change.* A rating scale for clinical trials must be sensitive to treatment- induced symptom change but to date we have a limited evidence-base to determine the precise sensitivity to change of currently used apathy rating scales and what effect size represents clinically significant change.
5 *Time-frame of assessment.* The different rating instruments for apathy measure symptoms within different specific periods, typically ranging between 1 week to 1 month. While this can be acceptable for a cross-sectional assessment of apathy severity, scales intended for use in clinical trials should consider the time necessary to observe clinically significant changes after the introduction of the tested intervention.
6 *Information source and type of rater.* Current apathy rating scales obtain information directly from the patient, caregiver (professional or informal)/study partner, clinician evaluation, or a combination of these. There is a consensus that in cognitively impaired individuals self-administered rating scales should not be used, especially in clinical trials, due to bias imposed by the symptom itself and difficulty of patients to rate changes in themselves; frequently, patients lack insight into their deficits (anosognosia). Instruments based on caregiver input and direct patient observation/assessment are preferable.
7 *Setting.* Apathy is commonly linked to disorders affecting older persons, some who may be institutionalized. While the process of institutionalization can lead to apathy, the institutional environment, which can be highly organized and directive, also poses peculiarities and differential aspects that can affect many behaviors, including apathy.

Regarding NPS measurement in preclinical and prodromal populations, and incorporating the framework set out in the ISTAART-AA criteria, the MBI checklist (MBI-C) has been developed specifically as a case ascertainment instrument for MBI.[36,80] The MBI-C is available in multiple translations at www.MBItest.org, and has potential utility in dementia prevention trials. The MBI-C is a general psychopathology scale, designed to detect NPS in pre-dementia populations. Apathy is reflected in the MBI-C with 6 questions: 2 each with respect to cognitive, behavioral and emotional apathy,[36] developed *a priori* to map onto the 3 domains for the apathy clinical criteria. With more robust queries for apathy symptoms and focusing on apathy as a syndrome in pre-dementia

populations, the MBI-C may provide an avenue to explore further the prevalence and prognostic utility of apathy in older adults with normal cognition, SCD and MCI. The MBI-C has been validated in CN, SCD and MCI for in-person, telephone and online administration.[50,81,82]

Research into apathy amongst cognitively unimpaired older adults (i.e., NIA-AA Stage 2 disease) with AD is still emerging. However, it has been limited by the challenges of confirming AD pathology in cognitively normal older adults, and by appropriate neuropsychiatric symptom measurement to determine case positivity for apathy. A recent study of amyloid+ cognitively unimpaired older adults (i.e., Stage 2 disease) found a relationship between global MBI-C score and tau uptake in early Braak regions associated with AD. While affective dysregulation and impulse dyscontrol predicted tau, apathy score demonstrated only a trend level of association ($P = 0.09$) in this sample.[58] It is not yet clear if the presence/absence of apathy symptoms, or scores above a specific threshold would provide more accurate prevalence estimates in this population. Further, many studies only report mean scores for the sample, rather than prevalence.[56,83,58] Further research is required.

Apathy has also been linked to important geriatric risk markers including hearing impairment and frailty. A study of older adults referred for audiometry found a link between MBI-C score and hearing impairment. Specifically, patients with hearing impairment had greater global MBI-C burden, and these findings were significantly higher for the apathy and impulse dyscontrol domains, emphasizing the clinical relevance of apathy in advance of dementia.[84] Similarly, MBI has been linked to frailty in a sample of elderly primary care patients with CN or MCI. In that recent study, the MBI-C composite score was associated with frailty, and those with apathy, affective dysregulation, and social inappropriateness were more likely to meet frailty criteria.[85]

Summary: The selection of the measurement tools of apathy in AD or other NCD is central to the design of pharmacological or non-pharmacological clinical trials for the treatment of apathy. Researchers should choose a tool with robust psychometric properties that is not exclusively based on information given by the patient, includes the usual apathy domains, is sensitive to change within the time-frame necessary to see treatment effects, that is preferably disease-specific and appropriate for the place (home or institution) where the patient lives. Unfortunately, none of the currently used scales meets these requirements and there is no widely accepted gold-standard assessment instrument. Detection of emergent apathy with the MBI-C is relevant given that syndromic apathy domains are measured, and scalable, as the rating scale is free and validated for multiple modes of administration.

Assessment methods based on Information and Communication Technologies (ICT) offer a novel and more ecological way of evaluating aspects and dimensions of apathy.[86,87] Actigraphy and methods used to monitor motor activity and rest-activity rhythms have also been shown to be useful, although do not address all apathy domains. Several actigraphy studies report the association of apathy in AD with diminished motor activity.[88–90] Other methodologies, like voice analysis, video analysis, or "serious games" are also being researched, with promising evidence emerging that has shown the utility of "serious games/interest games" to differentiate apathetic from non-apathetic individuals,[87] and machine learning speech analysis to be a reliable biomarker to detect/assess apathy and its subdomains.[91]

Although the NPI-Apathy item is the most frequently used tool, it is too simple for the task and does not accomplish many of the aforementioned requirements. Better assessment scales alternatives are the AES and the Dementia Apathy Interview and Rating, but both have limitations. Until further research brings new advancements in the area, we recommend using more than one assessment scale in the trial design and, when possible, including a measurement method different from rating scales, such as actigraphy. While the combined use of rating scales and actigraphy has to date never been done in treatment trials, its combined implementation is needed to determine efficacy. As a next step, the ability of scales to measure different dimensions of apathy in the diagnostic criteria need to be established.

MECHANISMS AND BIOMARKERS

The mechanisms and biomarkers underpinning apathy as a treatment target in pre-dementia and dementia populations remain poorly understood. Different underlying disease processes and disruption of

different neurocircuit pathways can result in the same phenotypic expression of apathy.

Neuroimaging correlates of apathy consistently show involvement of the medial frontal cortex and subcortical structures, including the anterior cingulate cortex, medial orbitofrontal cortex and ventral striatum.[35,92] Given the regular involvement of these structures in the development of apathy across a variety of neuropathologic disease processes, disruptions of functional neurobiological systems may be more important than specific molecular pathologies.[93]

The role of mechanisms and biomarkers are important when considering apathy as a treatment target in pre-dementia and dementia populations. Research on *pre-dementia populations* shows that subjects with MCI or prodromal-AD demonstrate a different pattern of hypometabolism on F18-fluorodeoxyglucose positron emission tomography (FDG-PET) (parietal-temporal cortex and posterior cingulate cortex) than seen in the dementia stage of AD (medial frontal regions). In 65 MCI ADNI subjects (11 apathetic; 54 apathy-free)[94] the apathetic group showed decreased metabolism in the posterior cingulate cortex. Gatchel et al.[95] analyzed the relationship of regional brain glucose metabolism with F18-FDG-PET to apathy in a larger ADNI cohort, finding both cross-sectional and longitudinal correlations between high apathy scores and posterior cingulate hypometabolism. Baseline supramarginal gyrus (lateral parietal) hypometabolism was also found to be directly correlated with the rate of change in apathy. Interestingly, in these MCI populations, unlike those in AD dementia studies, there was no association between apathy and glucose hypometabolism in medial frontal regions.[96,97] Lower inferior temporal cortical thickness in amnestic MCI patients with apathy is reported.[26,98] Guercio and colleagues[98] linked greater apathy to lower inferior temporal cortical thickness and greater anterior cingulate cortical thickness, while Donovan et al.[26] reported reduced baseline inferior temporal cortical thickness to predict increased apathy over time. CSF biomarkers did not relate to apathy severity.

In *AD dementia populations* apathy is most consistently implicated with frontal-subcortical reward circuits,[34,79,99] with anterior cingulate cortex dysfunction most frequently associated with apathy.[100] Multiple cross-sectional studies in mild to moderate AD dementia examined the association between apathy and neuroimaging measures, including hypoperfusion on SPECT, hypometabolism on FDG-PET, atrophy (cortical thinning/decreased volume) on structural MRI, and loss of white matter integrity (decreased fractional anisotropy) seen with diffusion tensor imaging. The most common region implicated has been the anterior cingulate cortex unilaterally or bilaterally.[96,101–107] Other frontal regions implicated include the orbitofrontal cortex[72,96,103,105,107–110] and dorsolateral and medial frontal cortices.[101,102,108,109] A few studies have implicated the insula,[110,111] parietal lobe,[104] thalamus,[96,104] and basal ganglia.[102]

Some studies have looked at the cross-sectional relationship between apathy and connectivity using resting-state functional MRI or FDG-PET in AD dementia. These show an association between apathy and decreased default mode network connectivity, increased salience network (ventral attention network) connectivity, and either decreased or increased fronto-parietal control network (central executive network) connectivity.[109,112,113]

Regional hypoperfusion and hypometabolism: Associated neuroimaging findings of AD dementia include patterns of hypoperfusion and hypometabolism in several frontal regions. A study of AD dementia patients measuring perfusion with ^{99m}Tc-labeled bicisate (ECD) single PET showed negative correlations of apathy symptoms - specifically lack of initiative, lack of interest and emotional blunting - with brain perfusion of the right anterior cingulate cortex, the right middle frontal orbital gyrus and the left superior dorsolateral prefrontal cortex, when controlling for depression.[108] Using F18 FDG-PET, Marshall and colleagues[96] demonstrated a definite association of apathy in AD dementia with hypometabolism in the bilateral anterior cingulate cortex and the medial orbitofrontal cortex, and a possible association of apathy with hypometabolism of the medial thalamus when controlling for age, education, cognitive symptom duration, depressed mood and delusional thought. Moreover, the individual cognitive, behavioral and emotional domains of apathy in AD dementia may be associated with distinct patterns of regional hypometabolism in medial thalamus, anterior cingulate, insula and temporal cortex.[97]

Regional atrophy: Studies examining apathy-related regional cortical atrophy in AD dementia consistently demonstrate atrophy of the medial frontal regions, including cortical thinning of the bilateral anterior cingulate cortex, left medial frontal cortex, bilateral

frontal cortex, head of the left caudate nucleus and bilateral putamen.[101,102] Tunnard et al.[105] partially verified these findings, demonstrating cortical thinning of the left caudal anterior cingulate cortex, the left lateral orbitofrontal cortex, and left superior and ventrolateral portions of the frontal regions.

More recently, Agüera-Ortiz and colleagues[114] found differing apathy-related brain damage in more advanced stages of AD dementia and between the three apathy domains using the APAthy in DEMentia Nursing Home scale.[115] In particular, they found that apathy severity was associated with bilateral damage to the corpus collosum and internal capsule; higher emotional blunting was linked to a smaller and more anteriorly located region of the right internal capsule and corpus collosum; and higher thinking deficits were linked to more ischemic damage in the right periventricular frontal region.[114]

Cortical tau depositions: Neuropathologic and in vivo tau deposition studies of apathy in AD dementia align with regional hypometabolism findings. Neuropathologic correlation of AD dementia patients with chronic apathy found high density deposition of neurofibrillary tangles in the anterior cingulate cortex (signifying tau burden), but not associated with neuritic plaques (signifying amyloid burden).[116] Another in vivo study of tau using flortaucipir PET showed associations between greater apathy and right anterior cingulate and dorsolateral prefrontal cortex tau burden in MCI and AD dementia, particularly in those with greater amyloid burden.[117]

Cortical beta-amyloid: The relationship of amyloid pathology to apathy is still being elucidated. Several primarily cross-sectional studies have focused on pathological markers of AD dementia assessed *in vivo* with CSF or PET imaging or post-mortem. One study failed to show an association between CSF ß-amyloid (Aß) 1-42, total tau, and phosphorylated-tau and apathy at baseline or over time across CN older adults, MCI, and mild AD dementia,[26] while another showed an association between apathy and CSF total tau and phosphorylated-tau, but not Aß 1-42.[118] However, Krell-Roesch et al.[119] reported 7.1 times higher odds of having apathy in MCI with amyloid deposition than MCI subjects without amyloid deposition. Similarly, Goukasian et al.[120] found amyloid positive MCI subjects to be more likely to develop apathy compared to amyloid negative MCI subjects.

A cross-sectional study of MCI showed a direct correlation between apathy and cortical amyloid burden, as measured by the Pittsburgh Compound B (PiB) tracer, irrespective of age.[121] In the same study, FDG-PET showed no relationship between apathy and regional hypometabolism. Mori and colleagues[122] studied a PiB-positive AD cross-sectional cohort and found apathy scores correlated with PiB deposition in the bilateral frontal cortex and right anterior cingulate cortex.

Neurotransmitters: Post-mortem, imaging and pharmacologic studies of apathy in AD dementia support the involvement of the cholinergic, dopaminergic (DA), serotonergic, GABA-nergic and noradrenergic neurotransmitter systems, all of which are affected by the AD dementia disease process.[33,123,124] Deficits in the cholinergic system are a well-known and a characteristic finding of AD dementia. A meta-analysis examining the efficacy of pharmacologic interventions for apathy in AD dementia reported a possible slight improvement in apathy for those who received cholinesterase inhibitors, suggesting that cholinergic deficits are an important target for apathy treatment.[33] PET studies of AD dementia patients have shown a trend for correlation between decreased nicotinic cholinergic receptor binding in the anterior cingulate cortex and apathy.[125] A subsequent analysis revealed similar findings: severity of apathy was associated with lower cholinergic receptor binding in bilateral middle cingulate and lateral orbitofrontal cortices.[126] Relationships were strongest for the behavioral domain of apathy and findings were not driven by anxiety or depression.[126]

Extensive serotonergic denervation in multiple locations including the raphe nuclei[127] and temporal cortex[128,129] has also been documented in post-mortem pathologic examinations of brain specimens with AD dementia. Alterations in 5HT-1A receptors and serotonin re-uptake (5HTT) sites within the hippocampus have been linked to agitation and depression in AD dementia, however the relationship is less clear with apathy.[130] The serotonergic system is known to inhibit cholinergic output and thus the cholinergic to serotonergic ratio of neurotransmission likely plays an important role in associated NPS.[131] Supporting this hypothesis are findings that selective serotonin re-uptake inhibitors (SSRIs) can induce an apathy syndrome in those with depression without AD

dementia[132] which can be reversed with discontinuation of the SSRI.[71] Thus far, study design and selective reporting make the effect of SSRIs on apathy in the pre-dementia and AD dementia populations difficult to interpret.[33]

Individuals with AD dementia have disruptions in DA neurotransmission between the basal ganglia, anterior cingulate and frontal cortex,[33,103] leading to impairment in the brain reward system. Apathy should be considered at least in part a hypodopaminergic syndrome based on the high prevalence of apathy (27%) seen early in the course of Parkinson's disease.[133–135] David and colleagues[136] reported on 14 AD dementia and 8 Dementia with Lewy Bodies (DLB) patients who were assessed clinically for apathy and for dopamine transporter (DAT) striatal uptake using[123] I-FP-CIT (DaTSCAN) SPECT. Lower DAT uptake correlated with greater apathy. More specifically, lower bilateral putamen DAT uptake correlated with lack of initiative.[136] However, another study showed no association with dopamine (D2/D3) receptor availability.[137] Nonetheless, dopaminergic deficits as a treatment target in apathy are supported by recent positive meta-analysis findings of three methylphenidate treatment studies of apathy in AD dementia.[33,138–140]

Noradrenergic and GABA-nergic systems are also potential treatment targets for apathy, but less is known about their involvement in AD-associated apathy. Noradrenergic and GABA-nergic neuronal loss is well described in AD dementia,[141–143] and these neurons are hypothesized to be co-transmitters with the serotonergic system.[143] Higher GABA plasma levels appear to be correlated with apathy.[124]

Fluid biomarkers: Two cross-sectional studies have looked at the relationship between serum biomarkers and apathy across MCI and AD dementia. One study showed an association with reduced brain-derived neurotrophic factor (BDNF),[144] while another study showed an association with increased tumor necrosis factor alpha (TNF-alpha), but no association with BDNF.[145]

Summary: Most studies examining the mechanisms and biomarkers of apathy in AD have been cross-sectional, focused on proxies of neurodegeneration, and looked at individuals with dementia. Those studies have primarily yielded a medial frontal localization in the anterior cingulate and orbitofrontal cortices. The few studies that examined people at earlier stages of AD (MCI or CN older adults at risk for AD dementia) and/or followed individuals longitudinally have shown associations with parietal and inferior temporal regions usually implicated more generally in early stages of AD. The few studies that investigated pathologic markers of AD and apathy have shown associations with amyloid at earlier stages of AD and with tau at later stages. While apathy is suspected to be a disorder of monoaminergic neurotransmission, almost no studies have looked at its relationship using neurochemical imaging (e.g. norepinephrine receptors or transporters) or serum biomarkers including markers of monoaminergic neurotransmission.

Thus, taking these many studies into consideration, there appears to be a more consistent localization of apathy to frontal regions with biomarkers of neurodegeneration and tau later in the AD disease process. On the other hand, earlier in the disease process, there appears to be more of an association of apathy with regions implicated in early stages of AD and global amyloid burden, similarly implicated in early stages, which may not correspond to a true localization but rather a reflection of apathy also being an early symptom of AD. We therefore conclude that the use of biomarkers in clinical trials targeting apathy in AD requires more observational studies with longitudinal follow-up, earlier stages of AD, and pathologic and neurochemical markers of AD. Meanwhile, at the stage of dementia, structural MRI or FDG PET imaging, with anterior cingulate and medial orbitofrontal cortices serving as regions of interest, may provide reasonable biomarkers for clinical outcomes. For trials in preclinical AD or prodromal AD (MCI), the evidence for using a biomarker outcome is weaker but one could consider biomarkers that are generally consistent with early stages of AD dementia such as inferior temporal and parietal atrophy on MRI or globally elevated cortical amyloid on PET.

TREATMENT AND INTERVENTION EFFICACY

Apathy treatment includes a variety of pharmacologic and non-pharmacologic therapies. Currently, no clear guidelines exist.

Pharmacological

While accumulating biological evidence points towards apathy as a treatment target, clinical trial data remain very limited and recent systematic reviews found that apathy is rarely considered a primary outcome measure or an inclusion criterion.[11,146] Both reviews found that cholinesterase inhibitors (ChEIs) may be the best available choice for the pharmacological treatment of apathy in dementia.[11,146] As reduced cholinergic tone has been linked to apathy,[147] ChEIs might prove helpful.[148,149] While Ginkgo biloba was also found to be effective,[150,151] there was weaker evidence of efficacy of memantine for apathy (compared to a higher efficacy when treating agitation and irritability).[146,149]

Stimulants alone, or in combination with ChEIs are also beneficial when treating apathy.[138,140,152,153] In particular, the Apathy in Dementia Methylphenidate Trial (ADMET) - a multicenter, phase II, double-blind, placebo-controlled, 6-week, randomized trial (RCT)[140] investigating the safety and efficacy of methylphenidate 10mg - showed significant between-group differences on the apathy domain of the NPI. While this was not reflected in changes on the AES, a secondary analysis of ADMET reported cognitive benefits.[153] A phase III clinical trial is currently underway (ADMET II).[154]

A 12-week clinical trial involved male community-dwelling veterans living with mild AD dementia (DSM-IV criteria) receiving on average 19mg of methylphenidate (n=30) or a placebo (n=30).[139] Primary outcome was change in apathy scores on the clinician-rated version of the AES at treatment weeks 4, 8 and 12. Significant group mean differences in AES-Clinician version (AES-C) scores, after adjusting for baseline apathy, were found between the methylphenidate group and the placebo group and differences increased over time. Behavioral, cognitive and motivational domains of apathy improved at week 8, while the emotional domain improved at week 12.

Conversely, atypical antipsychotics should not be used for long periods[155] and antidepressants (e.g., SSRIs, Chlor-phenyl-piperazine, L-Deprenyl) failed to improve patients' apathy scores.[146,156–162]

A recent meta-analysis of double-blind, randomized, placebo-controlled trials investigating apathy as a primary or secondary outcome in AD dementia, assessed1) the safety and efficacy of pharmacotherapies for the treatment of apathy in AD dementia and 2) the effect on apathy of pharmacotherapies for other primary outcomes in the treatment of AD dementia.[33] Of 21 studies involving a total of 6384 participants, only four studies had a primary aim of improving apathy (three with methylphenidate[138–140] and one with modafinil.[163]) Table 4 summarizes the findings of this meta-analysis of the efficacy of methylphenidate and modafinil. In summary, methylphenidate improved AES scores compared to placebo with greater effect in trials >12 weeks, but had no effect on NPI-apathy scores (possibly due to smaller sample sizes). This highlights the urgent need for well-defined clinical criteria and assessment tools that are consistent. Insufficient evidence was found based on one very small study of modafinil on apathy as assessed by the *Frontal Systems Behavioral Scale* apathy subscale.

Ruthirakuhan and colleagues[33] concluded there was low or very low quality of evidence that ChEIs (6 studies), ChEI discontinuation (1 study), antipsychotics (2 studies), antipsychotic discontinuation (1 study), antidepressants (2 studies), mibampator (1 study), valproate (3 studies) and semagacestat (1 study) had any impact on apathy. Harrison et al.[164] recently reviewed 24 studies on pharmacological trials targeting apathy in various dementia types (10 in AD, 6 in Frontotemporal Lobar Degeneration/ Frontotemporal Dementia (FTLD/FTD), 4 in dementia or probable dementia and MCI, 1 in Parkinson's Disease Dementia, 1 in DLB, and 2 in unspecified dementia), finding inconclusive evidence for impact on apathy.

Other pharmacological agents have also been used to target apathy. Callegari et al.[165] evaluated the use of agomelatine for apathy in 24 participants with behavioral variant FTD with no history of depression. Agomelatine is a structural analogue of melatonin and has antagonistic effects on melatonergic receptors and the 5-HT2C serotonergic receptor.[166] It is approved for use in major depressive disorders and is used to treat disrupted circadian rhythms.[167] The authors hypothesized that agomelatine could reduce apathy by restoring prefrontal dopaminergic and noradrenergic tone via 5-HT2C antagonism. To control for potential effects via the melatonergic system, melatonin was used as the control treatment for 10 weeks, followed by a 10-week crossover period. Agomelatine, but not melatonin, treatment was associated with significant decreases in AES, even when controlling for NPI-depression score and also in caregiver-

TABLE 4. Efficacy of Methylphenidate and Modafinil Targeting Apathy

	Outcomes	Anticipated Absolute Effects* (95% CI)		Relative Effect (95% CI)	Number of Participants (studies)	Quality of Evidence (GRADE)	Comments
		Risk with Placebo	Risk with Methylphenidate				
Methylphenidate	Change in apathy (AES score) assessed with: AES Scale from: 0 to 42 follow-up: range 2 wks − 12 wks	The mean change from baseline in apathy was -4.2 − 0.6	MD 4.99 lower (9.55 lower to 0.43 lower)		145 (3 RCTs)	LOW[a,b]	AES: Limited data on clinically meaningful changes
	Change in apathy (NPI-apathy subscale score) assessed with: NPI-apathy subscale Scale from: 0 to 12 follow-up: 2 wks − 6 wks	The mean change from baseline in apathy -2.6 − -1.69	MD 0.08 lower (3.85 lower − 3.69 higher)		85 (2 RCTs)	LOW[a,b]	1- to 2-point change suggested to be clinically significant in people with a clinically significant apathy[140]
	Adverse events assessed with: Number of participants reporting ≥ 1 adverse event follow-up: 2 wks − 12 wks	Study population 534/1000	 684/1000 (358 − 1,000)	RR 1.28 (0.67 − 2.42)	145 (3 RCTs)	LOW[a,b]	
	Change in NPS assessed with: NPI Scale from: 0 to 144 follow-up: 2 wks	The mean change from baseline in NPS was -2.08	MD 0.16 higher (7.89 lower − 8.21 higher)		25 (1 RCT)	LOW[a]	4-point change suggested to be clinically significant
	Change in cognition assessed with: MMSE Scale from: 0 to 30 follow-up: 2 wks − 12 wks	The mean change from baseline in cognition was -1.08 − -0.3	MD 1.79 higher (0.53 higher − 3.05 higher)		145 (3 RCTs)	MODERATE[a]	MMSE: 2- to 4-point change suggested to be clinically significant
	Change in functional performance assessed with: ADL scale Scale from: 0 to 6 follow-up: 12 wks	The mean change from baseline in functional performance was 0.4	MD 0.50 higher (0.39 lower − 1.39 higher)		60 (1 RCT)	MODERATE[c]	Limited data on clinically meaningful changes
	Change in functional performance assessed with: IADL scale Scale from: 0 to 8 for women, and 0 to 5 for men, to avoid potential for gender bias follow-up: 12 wks	The mean change from baseline in functional performance was -0.6	MD 2.30 higher (0.74 higher − 3.86 higher)		60 (1 RCT)	MODERATE[c]	Limited data on clinically meaningful changes
	Change in global disease severity assessed with: ADCS-CGIC or CGIC follow-up: 2 − 6 wks	Study population 116/1000	 65/1000 (17 − 244)	RR 0.56 (0.15 − 2.10)	85 (2 RCTs)	MODERATE[a]	
	Dropouts assessed with: Number of participants who dropped out prior to study completion. follow-up: 2 wks − 12 wks	Study population 41/1000	 86/1000 (25 − 303)	RR 2.10 (0.60 − 7.38)	145 (3 RCTs)	LOW[d]	
		Risk with placebo	Risk with Modafinil				
Modafinil	Change in apathy assessed with: FrSBe-apathy subscale (T-score converted from raw score) Scale from: 14 to 70 (raw score) follow-up: mean 8 weeks	The mean change from baseline in apathy was -6.82	MD 0.27 higher (3.51 lower − 4.05 higher)		22 (1 RCT)	LOW[a]	Limited data on clinically meaningful changes on the FrSBe apathy score

Note. Table of efficacy adapted from Ruthirakuhan et al.[33] As in Ruthirakuhan et al.[33]

*denotes the risk in the intervention group and its 95% confidence interval based on assumed risk in the comparison group and relative effect of the intervention (and its 95% confidence interval); GRADE Working Group Grades of Evidence:

[a] denotes quality downgraded one level due to imprecision (wide 95% confidence interval)

[b] denotes quality downgraded one level due to inconsistency (substantial heterogeneity was present

[c] denotes quality downgraded one level due to imprecision (only one study, with a relatively small sample size)

[d] denotes quality downgraded two levels due to very serious imprecision (very wide 95% confidence interval).

rated NPI-apathy and NPI-distress scores. Switching from melatonin to agomelatine was associated with a decrease in AES score, while the reverse was associated with an increase in AES. In the largest RCT using bupropion (150mg per day) - a norepinephrine - dopamine reuptake inhibitor - to treat apathy in 54 non-depressed patients with dementia of the Alzheimer Type (mean MMSE=19.3), the drug failed to improve apathy as measured by the AES-C over a 12 week period when compared with the placebo.[168] Interestingly, secondary analyses focusing on apathy subdomain factors of the AES scale showed significant worsening of the emotional apathy factor in the bupropion group after 12 weeks, whereas no significant differences were found between the groups for the other two factors.[168] Furthermore, the multi-center, placebo-controlled, crossover trial with bupropion[169] for the treatment of apathy diagnosed with the Structured Clinical Interview for Apathy-Dementia in Huntington's dementia failed to reveal significant differences in AES-informant scores between the groups.

Summary: There are no established treatments for apathy to date. A key factors limiting informative conclusions and the formation of advice include the small study sample sizes and study designs being utilized. To improve the quality of evidence for pharmacological treatment, future studies need to address the current trial design limitations and challenges, by 1) utilizing and validating the recently revised diagnostic criteria of apathy as a treatment target outcome; 2) include neurobiological, neurochemical and neuroimaging endpoints to help identify pharmacological treatment target endpoints; 3) inclusion of cognitive and functional outcome measures to investigate the secondary benefits of targeting apathy; and 4) utilize longer study durations and adequately powered studies to investigate the impact of pharmacological treatment on clinically significant apathy as a primary outcome measure.[33]

Non-Pharmacological

Non-pharmacologic interventions, specifically individualized therapeutic activities,[68] have shown promise in treating apathy. Goris and colleagues'[170] systematic review found that in institution-based settings music therapy, tailored personal contact, cognitive stimulation therapy, multi-sensory behavior therapy (including Snoezelen), group art therapy and therapeutic conversation all showed promise in reducing apathy, with the strongest evidence for *music therapy* (alone or in combination with other components). Most studies delivered at least 30-minute interventions for at least 10 sessions.[170] Exercise/activity interventions have also been shown to be effective.[171,172] Challenges noted included heterogeneity between studies, methods used to engage the person with dementia in the activity, apparent target of therapeutic effect (i.e. behavioral, emotional or cognitive domain of apathy) and extent to which interventions were tailored to specific individuals.[170] **Table 5** summarizes the efficacy of non-pharmacological interventions targeting apathy with several studies showing at least some benefit of non-pharmacological interventions for apathy. However, there were methodological challenges.[173] Apathy was a secondary outcome in more than half of the 37 studies included and tools used to assess apathy were often neither validated nor appropriate for the setting.[173]

Promising studies targeting apathy using non-pharmacological interventions are underway. One such area is the use of neurostimulation such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). Several mechanisms are proposed for the efficacy of these non-invasive neuromodulation techniques against apathy, including neuronal stimulation, increased cerebral blood flow, release of dopamine and neurotrophic effects. One preliminary study is evaluating the efficacy of a combination of tDCS and cognitive training.[174] High frequency rTMS, an FDA-approved treatment for refractory depression, of the dorsolateral prefrontal cortex has also been tested for the treatment of apathy as it can increase local cortical excitability. rTMS is FDA-approved for treatment resistant depression. A double-blind, randomized, sham-controlled, cross-over study of rTMS has been conducted in nine subjects with apathy and MCI, demonstrating significant improvements in apathy scores using the AES-C for rTMS compared to the sham.[175] Adverse events, which were mild and transient, did not differ between the arms.[175] Another double-blind, sham-controlled, parallel arm, randomized study of rTMS in older subjects with Alzheimer's dementia and apathy (N=20) showed significant improvement in motivation for rTMS compared to sham treatment after twenty treatments.[176] Additionally, there was also significantly greater improvement

TABLE 5. Efficacy of Non-Pharmacological Interventions Targeting Apathy

Intervention:	Effects:	Number of Participants:	Comparison Groups:	Effect Sizes:
Stimulation Retreat Model of Care	Increased external engagement; improved lack of interest and lack of initiative[195], but not statistically significant.	2 Units of 51 participants each	Experimental vs Control Group	Not reported.
Simulated Presence - a personalized audiotape approach	Improved withdrawn behavior; increased level of interest.[196]	54	Stimulated presence vs usual care	Improved withdrawn behavior 69% ($p < .001$) of the time; was significantly better than usual care (55%; $p < .001$); improvement occurred nearly twice as often compared to placebo (34%; $p < .001$).
Multi-Sensory Stimulation	Improved lack of interest and initiative.[197,198]	[197]: 50 [198]: 136	Multi-Sensory vs activity group	[197]: MD in total score: -3.72, 95% CI -7.1 to -0.34; $p = .032$. [198]: -0.4 points in apathy (SD = 1.1, 95% CI -0.9 to 0.1; $p < .05$) in the severely impaired group.
Kit–Based Activity Intervention	Improved lack of interest and initiative,[199] but not statistically significant.	37	Kit-based activity vs time and attention control	Not reported.
Recreational activities derived from the *Need–-Driven Dementia–Compromised Behavior Model*	Improved emotional blunting.[200]	30	1 of 6 possible order-of-condition presentations	MD in emotion sub-score = 10.71, SD = 7.2, 95% CI 8.5 − 13.0.
Live Interactive Music	Positive engagement effects; improved lack of interest and initiative).[201] However, these improvements were not found in another recent review of 38 trials evaluating the efficacy of receptive music therapy for apathy as a secondary outcome.[202]	[201]: 32 [202]: 38 trials involving 1418 participants	[201]: Live interactive music, passive pre-recorded music or silence. [202]: Diverse	[201]: Not reported. [202]: No significant difference: $I^2 = 97\%$, MD = -1.48, 95% CI -3.86 − 0.89.
Multisensory Behavior Therapy - Snoezelen	Improved lack of interest[203] and apathetic behaviour.[204]	[203]: 24 [204]:125	[203]: Multi Sensory Behavior Therapy vs structured activity session [204]: Experimental: 24-h Snoezel program vs control group: usual nursing home care	[203]: MD (SD) in apathy group vs. control group: 22.2 (7.85) vs 32.13 (9.79). [204]: Change score: 1.25, $\chi^2 = 5.15$; $p < 0.05$.
Reminiscence Group Treatment	Immediate improvements on the behavior and cognition subscales of the MOSES in AD and particularly in vascular dementia patients.[205]	24	Reminiscence group program vs routine daycare program	Not reported.
Tailored Activity Program	Improved lack of interest and initiative.[206]	60 dyads	Occupational therapy intervention with customized activities	Cohen's d = .61 for activity engagement, $p = 0.029$.
Music and Art Therapy and Psychomotor Activity	Improved engagement.[207]	146	Initial intervention (music and art therapy and psychomotor	MD = 0.21, 95% CI 0.07 to 0.34, $p < 0.005$.

(*continued on next page*)

TABLE 5. (*continued*)

Intervention:	Effects:	Number of Participants:	Comparison Groups:	Effect Sizes:
			activity) vs initial control (free activities in the day room)	
Activities Tailored to Functional Level and Personality Style of Interest	Improved passive behavior and engagement when in "personality style of interest" type of activities.[208]	128	Activities adjusted to functional level (FL) vs personality style of interest (PSI), vs FL+PSI, vs active control	PSI: Least Square Means = 18.48, 95% CI 17.3 to 19.6, $p < 0.005$. Functional Level + PSI: Least Square Means = 18.74, 95% CI 17.5 to 19.9, $p < 0.005$.
Brief Emotional Shaping Intervention	Improved lack of interest and initiative to "yes" responses to engage in activity.[209]	26 Alzheimer patients and 26 healthy controls	Positive conditioning vs neutral conditioning	$\eta_p^2 = .551$ for activity condition and $\eta_p^2 = .194$ for positive stimulus.
Progressive Muscle Relaxation Treatment	Improved interest, volition and social relationships.[210]	18 participants from 6 group home units	Progressive muscle relaxation vs control group (normal routine)	Not reported.
Individualized Cognitive Rehabilitation Intervention	Lowered apathy-related functional disability and delay institutionalization.[211]	40 sites including 653 outpatients	Standardized programs of cognitive training vs reminiscence therapy, vs individualized cognitive rehabilitation program vs usual care	Not reported.
Exercise/Activity	Significant improvement in apathy[171], and lower levels of apathy[172].	[171]: 14 [172]: 163	[171]: 3-month cognitive stimulation, physical activity, and socialization (Treatment Group) vs Usual activity (Control Group) [172]: 3-month intensive strengthening and balance exercises (Treatment Group) vs leisure activities (Control Group)	[171]: Mean change in AES in the treatment vs control group = 9.6 vs 0.4 ($P < .05$ for comparison with baseline scores) [172]: Cohen's d = 0.3 of the difference between groups in NPI apathy.

Note: The time frames in which the treatment effects were evaluated in the above studies varied greatly, ranging from immediately[197,198,201,203] to 2 years.[211]
MD: Mean difference; SD: Standard deviation; MOSES: Multi-dimensional Observation Scale for Elderly Subjects; PSI: Personality Style of Interest.

in cognition, function and clinical global improvement.[176]

Another RCT is evaluating the efficacy of a 20-session Cognitive-Behavioral-Treatment program compared to treatment as usual on depression and other NPS (apathy is a secondary outcome) in patients with mild AD, mixed AD and vascular dementia.[177] Further research is also emerging which demonstrates the efficacy of information and communication technology (ICT) approaches such as serious games to improve apathy.[178,179]

Recent recommendations for the use of non-pharmacological treatments for apathy have been published by Manera et al.[180] and highlight the suitability of non-pharmacological interventions as a treatment approach in a variety of neurocognitive and psychiatric diseases of all stages. They identify the importance of the presence of a therapist and/or caregiver to the effective delivery of non-pharmacological treatments, but also conclude that such interventions can successfully delivered in both clinical and home settings.[180]

Summary: Significant progress is being made in the understanding of non−pharmacological treatments for apathy, partly because they do not involve complex psychotherapy techniques, are quite safe and well accepted. However, they currently suffer from low implementation rates, relatively low participant engagement as the presence of apathy can interfere with treatment uptake, and low adherence to interventions. As Cohen−Mansfield and colleagues[181] highlight, personal attributes, environmental factors and stimulus characteristics may all contribute to the level and nature of a person's engagement. Therefore, the daily functioning of apathetic patients may be improved through direct prompting, visual cues and routines for daily activities.[182,183]

Validation methods utilized by non-pharmacological interventions differ from those implemented in pharmacological interventions, and several areas require much work, including: optimization of trial designs (especially in relation to randomization and blinding), training and use of interventionists, incorporation and consideration of premorbid personality/habits and person attributes into treatments, and contextual parameters for intervention.[184]

CURRENT ISSUES AND NEXT STEPS

Apathy in dementia has a substantial public health impact, and considerable progress has occurred in understanding pharmacological and non-pharmacological interventions. However, areas requiring improvement remain.

Diagnosis

Provisional diagnostic criteria have existed for over a decade specifying cognitive, affective and behavioral domains of apathy. However, there are concerns that important functional consequences of apathy are missing from this definition, that a domain of social interaction may be needed to be added and that cognitive and behavioral manifestations of apathy are challenging to distinguish in practice and may need to be combined. The recently published diagnostic criteria for apathy in neurocognitive disorders[37] provide a key step towards reconciling these differing approaches to nosology and the identification of different apathy cohorts and important apathy subdomains. Additionally, we need to account for the issue that current apathy definitions require that apathy be associated with functional impairment, which may be absent in MCI and MBI and by definition is absent in prodromal AD. These issues of apathy definition are particularly important to reduce the heterogeneity of participants in trials and maximize the odds of identifying benefit.

Symptom measurement

Developing effective treatments for apathy requires the use of scales with validation data demonstrating solid psychometric properties including reliability, validity, and sensitivity to change. The types of scales include general assessments of apathy, disease-specific measures including AD, and apathy assessments included in broader instruments such as the NPI. Instruments vary in their timeframe and type of rater, and we know little about the psychometrics of different instruments in different settings. Despite its widespread use and validation, we acknowledge the limitations of the NPI in its various forms, including the use of the NPI-Apathy item alone, as a general purpose assessment tool. The DAIR is currently the best-validated AD-specific instrument. We need to understand how the psychometric properties of instruments are affected by patient characteristics, particularly severity of dementia, overlap with other NPS, demographics, and care

setting (home vs. long-term care environment), and how the measures vary over time. It will be important to include apathy subdomains in future instruments, and to better understand how apathy affects caregiver burden and patient/caregiver quality of life.

Apathy in Pre-Dementia Stages

Increasing evidence suggests that late-life onset NPS may be prodromal to dementia, emerging in advance of cognitive deficits in some. One major innovation has been consensus development of a scale (MBI-C), which measures cognitive, behavioral, and emotional apathy in non-demented older adults. Further incorporation of the MBI-C into apathy observational and interventional studies will help in understanding the role of apathy as a dementia prodrome.

Mechanisms and Biomarkers

Apathy in AD dementia has been associated with structural and functional deficits of anterior cingulate cortex and medial prefrontal cortex, and also possibly thalamus and insula. However, the association of apathy with amyloid deposition and markers of early neurodegeneration is less clear. In MCI, there is evidence for apathy's association with deficits in posterior cingulate and with cortical thinning in inferior temporal and anterior cingulate cortices. However, we need better understanding of these mechanisms, particularly to incorporate apathy into interventions in prodromal and preclinical AD and related disorders.

We need more evidence from neurochemical imaging to identify key mechanisms and treatment targets. In AD dementia apathy was associated with lower cholinergic receptor binding in bilateral middle cingulate and lateral orbitofrontal cortices. Apathy may be associated with serotonergic neurodegeneration but to date the evidence is solely clinical. Data on the association of dopamine transporter levels with apathy are contradictory, with studies showing positive or null associations. There are no neurochemical studies to date on norepinephrine or other neurotransmitters and few longitudinal studies. There are data that apathy is associated with core AD fluid biomarkers such as levels of CSF tau, but few data on other fluid biomarkers.

There are urgent research needs to better understand biomarkers and polygenetic risk scores of apathy. More data are needed in MCI and healthy elderly at risk for AD dementia, addressing whether the associations with apathy in these groups is different from AD dementia, and whether there is a link and/or interaction with cognitive progression, amyloid or tau deposition. Polygenetic risk scores and other genetic contributions to apathy in AD have not been fully explored and may reveal important relationships and potential mediation by specific neurotransmitters, proteins, or other cellular variations. Multimodal imaging or fluid biomarkers may elucidate how different findings are related pathophysiologically. Other questions include: Are the neurobiological markers stable over time? Which among the neurobiological findings is ready for consideration as a biomarker for apathy in a clinical trial? Are there quantifiable measures that best represent key pathophysiologies? Which measures could be added to treatment trials to assess movement with an intervention and correlation with clinical effects? FDG-PET is promising in this area. We need to understand how best to incorporate biomarkers, behavioral measures, and novel digital biomarkers such as actigraphy.[88] There is an important unmet need for animal models of apathy to enhance preclinical drug development.

Proposal for an Observational Study of NPS in Dementia

The field could progress more rapidly by initiating a robustly powered observational study of NPS throughout the AD and related disorders spectrum, incorporating state-of-the-art NPS definitions and symptom scales and adding selected biomarkers. It would be important to maximize the generalizability and utility of such a study by 1) addressing cultural and genetic diversity in a multinational study design; 2) powering the study adequately to address the influences of demographic, clinical, and biomarker characteristics on measurement; 3) including preclinical and prodromal AD and related disorders populations, including cognitively intact older adults, and 4) incorporating a thorough biomarker assessment including structural and functional MRI, assessment of amyloid and tau pathology, monoaminergic PET where

available, and newer approaches to blood-based biomarkers such as neurofilament light chain, BDNF, inflammatory markers, blood-based assessment of amyloid and tau, and novel blood-based methodologies such as exosomes.[185] Such a study could direct participants to have imaging selectively according to symptoms, and could address *incident* NPS as an improvement over our current case-control designs. However, in the absence of such a study, the addition of apathy-specific instruments to ongoing and evolving large longitudinal studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the National Alzheimer's Coordinating Center (NACC) would be beneficial, particularly as both include samples with minimal cognitive deficits at study entry and both have robust sets of measures that can help elucidate biological mechanisms underlying apathy in AD. The recent addition of the Standardized Centralized Alzheimer's and Related Dementias Neuroimaging (SCAN) program to the NACC package provides an additional opportunity to evaluate longitudinal relationships between apathy and multimodal neuroimaging measures.

Treatments

Non-pharmacologic strategies are promising but the field is chaotic with many promising small studies. We need to understand how non-pharmacologic strategies are affected by stage of disease and symptom severity, patients' clinical characteristics, and the environment of care. Strategies that are most effective in a home environment may not be optimal for a long-term care environment and vice versa. Particularly in long-term care, attention should be paid to which interventions can be effectively performed in group settings, and in general we need to optimize dissemination of novel strategies.

A coherent approach to treatment development would examine the interaction of non-pharmacologic and pharmacologic strategies, such as a non-pharmacologic lead-in phase. The latter was incorporated into a multi-site trial of escitalopram for agitation in AD,[186] and in a 12-week trial of 10mg of donepezil in 272 patients with AD with clinically significant agitation who did not respond to a brief psychosocial treatment program.[187] We may similarly need to study combination pharmacological therapies. A better understanding is needed to improve the selection of clinical cohort populations in trials for better treatment outcomes.[188]

Other needs are to better understand the associations of clinical characteristics such as disease stage with response to interventions. This especially applies to using apathy and other NPS to enrich cohorts for preclinical and prodromal interventions. We need to incorporate our increasing knowledge of biomarkers into apathy trials to enrich cohorts (predictors of response) as well as surrogate markers of response. Trials need to be sufficiently powered to stratify analyses for relevant covariates including depression and other NPS, cognition, and environment of care. We need more novel approaches to pharmacologic interventions. We have been fortunate to have positive results from re-purposing a long-generic drug (methylphenidate) which has prominent dopaminergic and secondary noradrenergic agonism, but we need novel drugs that are more targeted to these and other mechanisms.

Finally, more insight is needed of how interventions affect the different aspects of apathy. The current absence of different apathetic symptom profiles and characterizations weakens the possibility to identify the specific target and efficacy of interventions. Considering diagnostic practice, it is important to better understand and identify sub-populations who may benefit more from tailored interventions. This requires the development of a harmonized apathy scale that reflects current clinical diagnostic criteria to support generalizability and comparability of findings.

CONCLUSION

We have made much progress in better understanding the role of apathy in affecting the impact and course of neurocognitive disorders, and are starting to see some successes in new treatments. Scientific issues that need to be addressed to progress further include better understanding apathy subdomains and biological mechanisms underpinning apathy through imaging and fluid biomarkers and targeting of psychosocial interventions. We propose the utility of a comprehensive multi-national longitudinal

observational study of NPS as a whole, incorporating the study of apathy.

AUTHOR CONTRIBUTIONS

Moyra E. Mortby: Substantial contributions to the conception or design of the work and the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST

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